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Developing and testing of a screening tool to predict people without IgE-mediated allergy: a quantitative analysis of the predictive value of a screening tool.

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Abstract

Background: Consultations in primary care for 'allergies' are common and it can be difficult to differentiate between IgE-mediated (atopic) symptoms which respond to allergen-specific interventions and those which are not without performing objective tests which are largely unavailable in UK general practice.

Aim: To develop and test a screening tool that can accurately discriminate between atopic and non-atopic individuals.

Design and Setting: Validation study in adult volunteers aged >16 years in Scotland.

Methods: The tool was developed using questions from a large cohort study and through consultation with experts. Participants answered the questions and had skin prick tests (SPT) to four aeroallergens (housedust mite, cat, dog, mixed grasses). Participants were classified as atopic if any average wheal diameter was ≥3mm greater than the negative control. Sensitivity, specificity, positive and negative predictive values of individual and combinations of questions were calculated.

Results: 143 participants completed the questionnaire and underwent SPTs. A total of 81 (56.6 %) were atopic. Negative predictive values for the individual questions ranged from 48.2% (55 not atopic /114 negative answers) to 72.0% (18/25). An optimum combination of four questions were identified, where a negative answer to all four questions was reported by 24 participants and 21 (87.5%) were not atopic.

Conclusions: We have identified a set of questions that correctly predict negative SPTs to common aeroallergens 88% of the time. These may be useful to exclude patients who do not warrant further investigation and who can reliably be advised that allergen avoidance is neither necessary nor helpful.

Keywords: atopy, skin prick test, general practice

How this fits in: The purpose of this study was to identify simple questions which can accurately predict the absence of atopy without the need for expensive and time-consuming objective tests e.g. skin prick tests or allergen-specific IgE blood tests. These questions can now be developed into a screening tool to be used by health care professionals and the general

public to exclude allergy. This will have the benefit of preventing unnecessary avoidance of allergens and could also be useful in excluding an allergic basis for adverse reactions to food which is extremely uncommon in those who are non-atopic.

Introduction

Allergic (IgE-mediated) disorders as a whole are responsible for substantial morbidity, healthcare utilisation and costs to the National Health Service (NHS).[1,2] In addition, there are significant numbers of people who mistakenly believe they are allergic and who utilise both NHS and their own time and resources pursuing unnecessary investigations (e.g. conventional skin prick testing (SPT) and specific IgE blood testing which are both associated with a high level of false positives[3]) and pursuing alternative 'allergy' testing (e.g. hair analysis or kinesiology which have no scientific basis), as a result of which they may unnecessarily avoid exposure to presumed triggers.[4]

However, it can often be difficult to differentiate between allergic (i.e. IgE-mediated) and non-allergic (i.e. non-IgE-mediated) symptoms. To date, the only way of identifying non-atopic status (defined as negative allergy tests to one or more airborne allergens and independent of clinical symptoms) is to do SPT or blood tests for the presence of specific-IgE. These diagnostic tests are, however, expensive (blood tests) and/or often unavailable in the primary care setting (SPT)[5]; they are furthermore difficult to interpret by generalist healthcare professionals and also people buying blood testing kits over-the-counter because of the high rate of false positives. A less common manifestation of IgE-mediated disease is food allergy. Food allergy is commonly over-estimated, particularly among parents who often attribute childhood skin rashes (which are, for example, virally-induced) to food allergy. It is noteworthy that IgE-mediated food allergy is uncommon in those people who are non-atopic (i.e. not sensitised to common airborne allergens as shown by negative skin prick/specific IgE tests to those allergens); in a recent study, less than 0.2% of children who were non-atopic went on to test positive to one of 12 food allergens.[6] In adults, 10-12% of the general adult population think they have some type of food allergy or intolerance[7, 8] whilst IgE-mediated food allergy can only be confirmed in 1-2%.[6] This represents a five-fold over-estimation of food allergy which is likely to have significant cost and societal implications.[1, 9]

Developing a screening tool to exclude allergy so that people who are non-atopic can be identified, either by themselves or by their nurse or doctor, could bring significant resource and health benefits. A simple, inexpensive, non-invasive method of screening would have the potential to reduce non-essential testing and referral (and therefore reduce healthcare utilisation and costs to the NHS) and to reassure patients as to the safety of continued exposure to allergens they wrongly suspect of causing their symptoms. Similar studies using a diagnostic tool to exclude disease in other medical fields include the use of D-Dimer test in patients with suspected venous thromboembolism[10, 11], and the serum levels of procalcitonin as a marker for bloodstream infections.[12]

Data from a large paediatric cohort study (further discussed below) suggests that approximately 5-10 questions from the clinical history may accurately predict non-atopic status, but this requires testing in clinical practice to confirm utility.

The aim of this study was therefore to investigate whether key clinical questions could accurately identify patients who are non-atopic.

Methods

Ethical approval

Ethical approval was obtained from the South East Scotland Research Ethics Committee 02 (SES REC 02) and Research & Development management approval was obtained from NHS Lothian. Amendment approval to extend the recruitment to the general public was obtained (SES REC 02).

Participants

Study population

Adults aged >16 years registered with general practices, or members of the general public, in Lothian, Scotland were invited to participate in this study.

The exclusion criteria were:

- < 16 years old
- pregnancy
- uncontrolled asthma
- a previous history of anaphylaxis
- antihistamines in the previous 48 hours

- unwilling or unable to give informed consent.

Recruitment

The study was advertised in general practices, in liaison with the Scottish Primary Care Research Network. In the general practices, posters were displayed in the waiting area and flyers were handed out to people who expressed an interest. Flyers were also sent to patients attending designated asthma clinics. Email, posters and websites within The University of Edinburgh were used to inform the general public. Potential participants were asked to contact the researcher by phone or email and were sent the participant information sheet to read prior to their appointment. Participants were asked to book an appointment with the researcher for clinics at their GP surgery or in the Clinical Research Facility (CRF) at the Royal Infirmary Edinburgh (RIE). Consent forms were completed and exclusions criteria checked at the beginning of the appointment. Permission was taken for the results of the skin prick testing to be sent to the participant's GP.

Questionnaire development (Index test)

We utilised five questions identified from the Ashford Birth Cohort Study[13] as having the potential to accurately predict non-atopic status, but which had not been tested in clinical practice, as a basis for our questionnaire (see Box 1).

Box 1: Ashford Birth Cohort Study screening questions

1.	Do you have a personal history of hay fever?
2.	Do you have a personal history of asthma?
3.	Do you have a personal history of eczema or asthma as a baby (age <2years)?
4.	Do you have a personal history of other allergy?
5.	Do any of your parents or siblings have a history of hay fever?

Cullinan et al (2004)[13] defined atopy as a positive SPT (≥3mm) to at least one of mixed grasses, cat fur and house dust mite. Parents in the Ashford Cohort answered the five allergy questions and parents and children were skin prick tested. The numbers of people being 'non-atopic' in relation to each negative response ranged from 63-77%; i.e. if a parent said that they had no history of hayfever then they had a negative allergy test to grass 77% of the time (high negative predictive value). We amended the wording of these questions and supplemented them with six additional questions identified through consultation with experienced allergy clinicians as

also having the potential to discriminate between allergy and non-allergy. Five allergy clinicians were sent a short summary of the study prior to the consultation (see Appendix) and were asked to identify any additional questions which they felt were able to discriminate between atopy and non-atopy in someone presenting with suspected allergy. All questions were included and the final 11 questions are shown in Box 2.

Box 2: Questions used in screening tool

1. Are you aged less than 40yrs?
2. Do you have or have you ever had hay fever?
3. Do any of your parents or siblings (brothers or sisters) have or have ever had hay fever?
4. Do you have or have you ever had asthma?
5. Did you ever have eczema or asthma as a baby (aged less than 2 years)?
6. Do you have or have you ever had any other allergy?
7. Do you ever have any symptoms of itch or sneeze
8. Do your allergy symptoms vary when you go from place to place (e.g. on holiday)?
9. Is there a specific trigger that always sets off your allergy symptoms?
10. Do your allergy symptoms start within 30 minutes of being exposed to a specific trigger?
11. Do your allergy symptoms improve after treatment with anti-histamines?

Questionnaire completion

Consenting participants answered the resulting 11-question screening tool relating to their atopic status. Data were recorded anonymously on data collection sheets. Clinical information and index test results were not available to the assessors of the reference standard.

Skin prick testing (reference standard)

Skin prick testing was performed using positive (histamine dihydrochloride) and negative (allergen diluents) controls, mixed grass, house dust mite (*D.pteronyssinus*), dog and cat

allergens on the volar aspect of the forearm according to a standardised technique using individual sterile lancets. Skin wheal diameter (mm) was measured after 15 minutes using a measuring grid. Positive responses to allergen were defined as mean wheal sizes ≥3mm bigger than the negative control; negative responses were the same size or smaller than the negative control. Non-atopic status was defined as negative responses to all four skin prick tests; atopic status was defined as a positive response to ≥1 aeroallergen.

Data analysis

Using positive skin prick tests results as the gold standard for atopic status, sensitivity, specificity, positive and negative predictive values of the individual questions and combinations of questions were calculated. Confidence intervals (95%) were calculated for the sensitivity and specificity using standard methods for proportions. Positive and negative predictive values were calculated as the probability that the questionnaire responses agreed with the skin prick test results, where the positive predictive value was the proportion of patients with a positive history who were atopic and the negative predictive value was the proportion of patients with a negative history who were not atopic.

Logistic regression techniques were used to identify the combination of questions which demonstrated the strongest association with non-atopic status. Responses to all questions were considered individually; then a multivariate model was constructed by including the questions with the strongest associations one by one until no others questions significantly contributed to the fit of the final model. The contribution of each question was evaluated using likelihood ratio tests. Once these questions were identified it was possible to calculate the sensitivity, specificity, positive and negative predictive values for this combination of questions. Participants were defined as "questionnaire positive" if at least one response to these questions was positive and "questionnaire negative" if all responses were negative. All statistical analyses were undertaken using Stata (Stata Corporation, USA).

Sample size

Based on a sample size of 150, the specificity would be estimated with 95% confidence intervals of ± 4.8% for a specificity of 90%. The sample size was calculated using an online statistical tool.[14]

Results

143 participants completed the questionnaire and underwent skin prick tests; there were no adverse reactions. There were no indeterminate index or reference standard results or missing data. The mean age of participants was 41.1 years (range 18.8-84.9), and 76.9% were female. A total of 81 participants (56.6%) were atopic; the rates for each allergen were 62/143 (43.4%) for grass, 67/143 (46.9%) house dust mite, 49/143 (34.3%) for cat and 33/143 (23.1%) for dog. Individual question analysis is shown in Table 1.

We explored any correlation between questions, and whilst many of the questions were related to each other, none were in perfect agreement. Logistic regression techniques identified Questions 2, 8, 3 and 9 as being independently associated with the risk factor of being non-atopic (Table 2).

The negative response to Question 8 was the most associated with being not atopic (i.e. negative skin tests); after adjusting for the other questions, patients were four times more likely to have negative test results if they answered no to that question. Table 3 shows the relationship between the responses to these four questions and atopic status.

This comparison of the questionnaires and skin tests gave:

Sensitivity = 78/81 = 96.3% (95% CI 89.6, 99.2)

Specificity = 21/62 = 33.9% (95% CI 22.3, 47.0)

Positive predictive value = 78/119 = 65.6% (95% CI 56.3, 74.0)

Negative predictive value = 21/24 =87.5% (95% CI 67.6, 97.3)

This shows that the combination of Questions 2, 8, 3 and 9 had a reasonably high negative predictive value; most (87.5%) of those who gave negative responses to all the questions were not atopic (had negative skin tests).

Discussion

Summary

We were able to identify four questions which were reasonably predictive of non-atopic status in patients with suspected allergy. This has the potential to be useful to differentiate between IgE-mediated and non-IgE-mediated symptoms (and so to drive treatment choices and avoidance advice) in primary care where diagnostic tests are not routinely available.

Strengths and limitations

We were able to recruit members of general practices and the general public for this work, and almost achieved our target sample size of 150. The screening tool is intended for use by health care professionals in primary care and the general population, which is where it was tested,[15] and was compared with the best gold standard available. Our definition of atopy, a positive skin prick test to common (country- and climate-specific) aeroallergens, has been used in other studies[13], and our choice of skin prick testing as a gold standard is safe and feasible for aeroallergens.[16] However, this definition of atopy gave a prevalence of 57% in our sample population, which is high compared with other similar studies, presumably because there was a higher motivation to participate amongst people who are atopic.[17] This may have resulted in loss of power to detect important questions that predict non-atopy.

One limitation is the sample size; in the detailed analysis, where combinations of questions were examined, the numbers were small, and increasing the sample population would have contributed more data to each combination of positive/negative to the skin prick testing and the questions, potentially increasing the negative predictive values and improving precision.

Due to the nature of recruitment, advertising with posters and leaflets, we were unable to record how many people saw the information but declined to take part, thus preventing any considerations of the representativeness of the findings.

Comparison with existing literature

Previous work in this field has mainly focussed on developing questions which can accurately predict sensitisation to a suspected allergen (i.e. do positive answers to clinical questions predict positive skin prick or specific IgE test results).[17-19] The focus of this current study, however, was different; we sought to identify simple questions for which 'no' answers could predict negative skin tests in a general population with a view to being able to assess atopic status without the need for a formal diagnostic test.

This combination of questions compares well to other studies that have reported a negative predictive value for atopy including ALATOP[20] in vitro multispecific IgE test which reported the following: 1) Sensitivity: 89.57%; 2) Specificity: 98.06%; 3) Positive predictive value: 98.65%; 4) Negative predictive value: 85.59% . Similarly, a study looking at the accuracy of allergy skin prick tests in predicting allergy[17], SPT was predicted to be positive in 42.6% and was positive in 36.1%. Depending on SPT results with the cut-off value 3 mm, prediction

sensitivity was 77%, specificity was 65.3%, positive predictive value was 65%, and negative predictive value was 86%. In studies of different diagnostic tests, Wang et al[11] reported a slightly lower sensitivity of 64% and a higher negative predictive value of 94%, concluding that the D-dimer assay may have a role in tailoring treatment to optimise prevention of venous thromboembolism. Similar results were found for the predictive value of procalcitonin in excluding bloodstream infections and managing antibiotic usage (83% sensitivity and 94% for negative predictive value).[12]

When a test has a high sensitivity, a negative test rules out the diagnosis[21], and our study reports a high sensitivity (96%) and negative predictive value (88%). We therefore think we can be fairly confident that this result using the 4 questions has a high negative predictive value (as it is almost 90%), although the numbers were relatively small.

Implications for practice

We were able to identify four questions which were predictive of non-atopic status. Our results provide useful data for the development of a screening tool for non-atopic status in people with suspected allergy, although the questions need further validation in a larger, independent population of consecutively enrolled patients. This would increase the numbers in the combination analysis and increase precision. The screening tool could then be confidently used by healthcare professionals or patients to accurately predict non-atopic status.

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Contributorship: VH and ED were the researchers employed on this study. SW was the principal investigator of the study, oversaw the delivery of the work and contributed to the

drafting of the manuscript. AS was a co-investigator on this study and commented on earlier drafts of the manuscript. JH was the statistician and carried out the statistical analysis.

Conflict of interests: All authors declare no conflicts of interests.

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Table 1: Validity of each question as a tool for identifying atopic status

Question	**Number (%) with negative response to question**	**Sensitivity % (95% ci)**	**Specificity % (95% ci)**	**Positive Predictive Value % (95% ci)**	**Negative Predictive Value % (95% ci)**
1. Are you aged less than 40yrs?	73 (51.1%)	53 (42-64)	56 (43-69)	61 (49-73)	48 (36-60)
2. Do you have or have you ever had hayfever?	73 (51.0%)	68 (57-78)	75 (63-86)	79 (67-87)	64 (52-75)
3. Do any of your parents or siblings (brothers or sisters) have or have ever had hayfever?	79 (55.2%)	59 (48-70)	74 (62-84)	75 63-85)	58 (47-69)
4. Do you have or have you ever had asthma?	96 (67.1%)	43 (32-54)	80 (69-90)	74 (60-86)	52 (42-62)
5. Did you ever have eczema or asthma as a baby (aged less than 2 years)?	114 (79.7%)	27 (18-38)	89 (78-95)	76 (56-90)	48 (38-58
6. Do you have or have you ever had any other allergy?	56 (39.2%)	69 (58-79)	50 (37-62)	64 (53-74)	55 (41-69)
7. Do you ever have any symptoms of itch or sneeze?	25 (17.5%)	91 (83-96)	29 (18-42)	62 (53-71)	72 (51-88)
8. Do your allergy symptoms vary when you go from place to place (e.g. on holiday)?	61 (43.0%)	75 (64-84)	66 (53-780	74 (63-83)	67 (54-79)

9. Is there a specific trigger that always sets off your allergy symptoms?	76 (53.2%)	62 (50-72)	73 (60-83)	74 (63-84)	59 (47-70)
10. Do your allergy symptoms start within 30 minutes of being exposed to a specific trigger?	64 (44.8%)	69 (58-79)	63 (50-75)	71 (60-81)	61 (48-73)
11. Do your allergy symptoms improve after treatment with anti-histamines?	58 (40.6%)	72 (61-81)	56 (43-69)	68 (57-78)	60 (47-73)

Table 2: Results from logistic regression (outcome is not atopy: i.e. negative skin tests)

Negative response to:	**Adjusted* Odds Ratio (95% ci)**	**p-value**
2. Do you have or have you ever had hayfever?	2.44 (0.99, 6.00)	0.05
8. Do your allergy symptoms vary when you go from place to place (e.g. on holiday)?	4.00 (1.67, 9.57)	0.002
3. Do any of your parents or siblings (brothers or sisters) have or have ever had hayfever?	3.19 (1.37, 7.44)	0.01
9. Is there a specific trigger that always sets off your allergy symptoms?	3.09 (1.32, 7.22)	0.01

*all odds ratios are adjusted for responses to the other three questions

Table 3: Responses to the four key questions and atopic status

	Skin prick test		
	Atopic	Not atopic	Total
Test (questions)			
Questionnaire positive	78	41	119
Questionnaire negative	3	21	24
Total	81	62	143

Questionnaire positive = At least one positive response

Questionnaire negative = all responses negative

Appendix: Study summary for allergy specialists

Developing and testing a screening tool to accurately predict non-atopic status in patients with suspected allergy

Background

Disorders such as asthma, rhinitis and urticaria are extremely common in Scotland, potentially affecting up to one in three of the population1. The commonest manifestations are respiratory and dermatological, and are often caused by exposure to allergens such as pollens and house dust mites mediated through the production of allergen-specific IgE antibodies and subsequent histamine release. Allergic (IgE-mediated) disorders as a whole are responsible for substantial morbidity, healthcare utilisation (over 4% of GP consultations and 1.5% of hospital admissions in Scotland are for allergic diseases) and costs to the NHS1. In addition, there are significant numbers of people who mistakenly believe they are allergic and who utilise both NHS and their own time and resources pursuing unnecessary investigations (e.g. conventional skin prick testing (SPT) and specific IgE blood testing which are both associated with a high level of false positives) and pursuing alternative 'allergy' testing (e.g. hair analysis or kinesiology which have no scientific basis), as a result of which they may unnecessarily avoid exposure to presumed triggers4. For example, 10-12% of the general adult population think they have some type of food allergy or intolerance7, 8 whilst IgE-mediated food allergy can only be identified in 1-2%6. This represents a five-fold over-estimation of food allergy which is likely to have significant cost and societal implications1, 9.

However, it can often be difficult to differentiate between allergic (i.e. IgE-mediated) and non-allergic (i.e. non IgE-mediated) symptoms. To date, the only way of identifying non-atopic status (defined as negative allergy tests to one or more airborne allergens and independent of clinical symptoms) is to do SPT or blood tests for the presence of specific-IgE. These diagnostic tests are, however, expensive and often unavailable in the primary care setting, and are furthermore difficult to interpret by healthcare professionals and also people buying blood testing kits over-the-counter. Negative allergy tests alone are a relatively accurate predictor of non-allergy22, although it is not clear at present whether a negative allergy history accurately predicts negative allergy tests.

Outline of this project

This study will investigate whether key clinical questions can accurately identify patients who are non-atopic. We propose to develop an instrument that is comprised of validated questions, which can identify those patients for whom an allergy test is so likely to be negative that it is not worth doing (i.e. a very high negative predictive value). This has the potential to be useful both for clinicians and patients in streamlining care in a cost-effective manner.

Collaboration with colleagues from Imperial College London has enabled us to analyse unpublished data from the Ashford Birth Cohort, providing useful information about parental and child allergy status. Parents answered the following five allergy questions and parents and children were skin prick tested:

1. Do you have a personal history of hayfever?
2. Do you have a personal history of asthma?
3. Do you have a personal history of eczema or asthma as a baby (age <2years)?
4. Do you have a personal history of other allergy?
5. Do any of your parents or siblings have a history of hayfever?

Atopy was defined as a positive SPT (≥3mm) to at least one of mixed grasses, cat fur and house dust mite. The numbers of people being 'non-atopic' in relation to each negative response ranged from 63-77%; i.e. if a parent said that they had no history of hayfever then they had a negative allergy test to grass 77% of the time (high negative predictive value). A negative response to <u>all</u> the questions was associated with a high rate of negative allergy tests in adults (83%). Results from the same study in children were similar (89%), however numbers were smaller. High specificity (ideally 95%) is required for the tool to be useful in clinical practice.

These five questions will be used as the basis for the screening questionnaire. Additionally, we will identify any other questions that, according to experienced allergy clinicians, discriminate between allergy and non-allergy and test them with the questions identified above to create the combination with the highest negative predictive value.

We now wish to find out which questions, addition to those listed above, discriminate between atopy and non-atopy in someone presenting with suspected allergy.

Name: _____

Position:_____

Questions:

1. _____
2. _____
3. _____